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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Charles T. Esmon and Jun Xu	Group Art Unit: 1636
Serial No.: 09/139,425	Examiner: Sumesh Kaushal
Filed: August 25, 1998	Atty. Dkt. No.: OMRF:066US/SLH
For: TARGETING OF MOLECULES TO LARGE VESSEL ENDOTHELIUM USING PCR	

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37 C.F.R. §1.8

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January 10, 2005
Date

Steven L. Highlander

APPEAL BRIEF

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APPEAL BRIEF

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-01450

Dear Sir:

This brief is filed (in triplicate) in response to the Office Action, mailed March 8, 2004, regarding the above-captioned application. This brief is due on December 10, 2004, by virtue of the Notice of Appeal received by the PTO on June 10, 2004. The fees for the brief are enclosed; however, should any other fees be due, or should appellants' check be missing, the Commissioner is authorized to deduct said fees from Fulbright & Jaworski L.L.P. Account No.: 55-1212/OMRF:066US/SLH. Please date stamp and return the attached postcard as evidence of receipt.

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I. Real Party In Interest

The real parties in interest are the assignee, Oklahoma Medical Research Foundation.

II. Related Appeals and Interferences

There are no related appeals or interferences.

III. Status of the Claims

Claims 1-25 are pending. Claims 1-25 are on appeal. The text of each claim on appeal, as pending, is set forth in an Appendix in this appeal.

IV. Status of the Amendments

The claims were last amended in the appellant's response mailed on May 12, 2003. An appendix set forth the claims on appeal.

V. Summary of the Claimed Subject Matter

The claimed methods and compositions are directed to selectively delivering a molecule to the nucleus of endothelial cells of the large vessels (page 2, lines 5-10), by administering a conjugate (page 2, line 12) of (1) an agent binding selectively to endothelial protein C receptor (EPCR) which promotes uptake by the cell and transfer into the nucleus and (2) the molecule to be delivered to large vessel endothelial cells (page 2, lines 20-24). The conjugate may be formed between the molecule to be delivered and an antibody to EPCR, activated protein C (page 2, lines 5-8). The conjugate may comprise a chimeric antibody (page 8, lines 18-24) binding to the molecule to be delivered and to EPCR (page 8, lines 5-24). The molecule to be delivered may be a nucleic acid molecule such as a gene or cDNA under the control of a promoter expressed in the nucleus of an endothelial cell and the nucleic acid molecule is delivered by directly contacting the endothelial cells of large vessels with the nucleic acid conjugate or by catheterization to the

endothelial cells (page 6, line 24 to page 7, line 17; and page 10, lines 9-27). The nucleic acid molecule to be delivered may be in the form of triplex forming oligonucleotides, ribozymes, guide sequences for ribozymes, and antisense (page 7, lines 1-3). Alternatively, the molecule to be delivered may be a drug, diagnostic agent, protein (page 7, lines 18-25), wherein the protein may be a transcription factor. The coupling agent may be streptavidin and biotin, or the agent may have multiple charges (page 2, lines 1-19). The conjugate may be delivered to large endothelial cells in culture or isolated from an individual (page 10, lines 1-4), or administered directly to an individual (page 9, lines 3-32).

VI. Grounds of Rejection to be Reviewed on Appeal

The issues presented on appeal are:

(1) Whether claims 1-25 are enabled as required by 35 U.S.C. §112, first paragraph;

(2) Whether claims 1, 4, 6-7, 10, 13, 14, 18, 19, 21-13 and 25 were properly rejected as lacking proper written description;

(3) Whether claims 7, 13, 14, and 19 are clear and definite as required by 35 U.S.C. §112, second paragraph;

(4) Whether claims 13, 15, 20 and 22 were properly rejected under 35 U.S.C. §102(b) as lacking novelty over U.S. Patent No. 5,225,537 to Foster *et al.* ("Foster");

(5) Whether claims 13, 15, 20 and 22-23 were properly rejected under 35 U.S.C. §102(b) as lacking novelty over U.S. Patent No. 5,571,786 to Eibl *et al.* ("Eibl"); and

(6) Whether claims 13-15, 20 and 22 were properly rejected under 35 U.S.C. §102(b) as lacking novelty over PNAS:10212-10216, 1996, by Stearns-Kurosawa *et al.* ("Stearns-Kurosawa").

VII. Grouping of Claims

The claims do not stand or fall together. The claims can be grouped as follows: (1) claim 1, directed to a method for selectively delivering a molecule to the nucleus of an endothelial cell of a large vessel *via* a conjugate comprising an agent binding to EPCR, (2) claims 2, 3, 4, and 10, directed to defining the conjugate of claim 1; (3) claims 5-9, directed to defining the molecule to be delivered; (4) claims 11-12, directed to defining a target for administering the conjugate; (5) claims 13, 14, 15, and 25, directed to compositions of conjugates that bind selectively to EPCR; (6) claims 16-21, directed to defining the molecule to be delivered of the conjugate; (7) claims 22-24, directed to defining the coupling means of the conjugate. Reasons for this grouping and arguments for the separate patentability of these groups of claims are provided below.

VIII. Arguments

(a) The Claimed Invention

The claimed methods and compositions are directed to selectively delivering molecules to the nucleus of endothelial cells of the large vessels, by administering a conjugate of (1) an agent binding selectively to endothelial protein C receptor (EPCR) which promotes uptake by the cell and transfer into the nucleus and (2) the molecule to be delivered to large vessel endothelial cells. The conjugate binds to the EPCR, the conjugate is endocytosed, and the molecule is thereby delivered to the cytoplasm or to the nucleus of the large vessel endothelial cells (see claim 1 as originally filed and the Examples set forth in the specification). The conjugate may be delivered by directly contacting the endothelial cells of large vessels with the conjugate or by catheterization of blood vessels formed by the endothelial cells (page 10, lines 15-18).

(b) Rejection Under 35 U.S.C. §112, First Paragraph

i. The Legal Standard for Enablement

The Court of Appeals for the Federal Circuit (CAFC) has described the legal standard for enablement under §112, first paragraph, as whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art, without undue experimentation (*See, e.g., Genentech, Inc. v. Novo Nordisk A/S,* 108 F.3d at 165, 45 USPQ 2d at 1004 (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ 2d 1510, 1513 (Fed. Cir. 1993); See also *In re Fisher,* 427 F.2d at 839, 166 USPQ at 24; *United States v. Telectronics, Inc.*, 857 F.2d 778 (Fed. Cir. 1988); *In re Stephens*, 529 F.2d 1343 (CCPA 1976)). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation (*M.I.T. v. A.B. Fortia,* 774 F.2d 1104 (Fed. Cir. 1985)). In addition, as affirmed by the Court in *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524 (Fed. Cir. 1987), a patent need not teach, and preferably omits, what is well known in the art.

Whether the disclosure is enabling is a legal conclusion based upon several underlying factual inquiries. See *In re Wands*, 858 F.2d 731, 735, 736-737, 8 USPQ 2d. 1400, 1402, 1404 (Fed. Cir. 1988). As set forth in *Wands*, the factors to be considered in determining whether a claimed invention is enabled throughout its scope without undue experimentation include the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims. In cases that involve unpredictable factors, "the scope of the enablement obviously varies inversely with the degree of unpredictability of the factors involved." *In re*

Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The fact is that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation "must not be unduly extensive." *Atlas Powder Co. v. E.I. DuPont De Nemours & Co.*, 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984). There is no requirement for examples.

ii. Rejection of Claims 1-25 Under 35 U.S.C. §112, First Paragraph

The invention is the discovery that molecules, which are bound by EPCR on cells, are taken up by the cells and can thereby be transported into the nucleus. This is demonstrated in the application with respect to one molecule: an antibody to the EPCR receptor. Throughout prosecution, many articles have been cited to support the Examiner's assertion that gene therapy is not enabled. However, no evidence for why results obtained with an antibody to the receptor would not be predictive of other molecules which also bind to the receptor. It is important to note that the claims on appeal are limited to conjugates of molecules which bind to the EPCR. This binding causes uptake of the conjugates into the cell. The claim language excludes those molecules which are not conjugates that cannot be taken up by the cell(s). All of the other components used in the claimed invention are routine, including the molecules to be delivered, and the means for coupling a molecule to an EPCR binding agent. Such means are well established in the art and include covalent or ionic interactions, chemical coupling, for example, succinic anhydride; chimeric proteins or protein fusions. Indirect binding may be accomplished *via* an intermediate molecule like streptavidin or biotin, or *via* a positively charged polymer like lysine, pyrrole, or chitosan. Coupling means, such as those described above, were well known in the art at the time of filing of the present application.

The Examples in the specification clearly show that the claimed methods were *actually reduced to practice.* Example 2 discusses the visualization of EPCR mAb nuclear translocation into the nucleus, wherein the EPCR mAb is conjugated to biotin. FIG. 2 is a graph of ^{125}I streptavidin nuclear delivery *via* biotinylated anti-EPCR mAb. These results demonstrate that the streptavidin conjugates can be delivered to the nucleus *via* EPCR (see Example 4). Example 6 interestingly shows the uptake of biotin, *via* EPCR, in the presence of serum, thereby presenting an obvious case for clotting mechanisms driving therapeutic molecule uptake through the EPCR. In each of the above-identified examples, the common mechanism of delivery to the nucleus is the EPCR. One of ordinary skill in the art will readily recognize that EPCR binding results in consistent and efficient nuclear delivery.

Throughout prosecution, the applicants have submitted references that clearly show that gene therapy was proven to be successful in the treatment of endothelial cells. For example, Baumgartner *et al.* (Circulation, March 31, 1998; see After Final Amendment and Response mailed on February 4, 2002) demonstrated therapeutic intramuscular gene transgene to endothelial cells in need of treatment using plasmid DNA encoding an endothelial cell mitogen. Baumgartner explicitly teaches successful gene therapy to endothelial cells. Baumgartner presents results from a phase I trial, "unanimously approved by the Recombinant DNA Advisory Committee and the U.S. Food and Drug Administration," and used to study new chemotherapeutic agents administered to human subjects. The data presented shows expression of the delivered gene (*via* protein level) as a transient peak of gene product in the systemic circulation one to three weeks after gene transfer (see FIG. 1 and description at page 1116 of Baumgartner). The data presented in the Baumgartner reference demonstrate that the state of the prior art, the relative skill of those in the art, and the predictability or unpredictability of the art

are such that a method for selectively delivering a molecule to the nucleus of endothelial cells of large vessels *via* selective binding to the endothelial protein C receptor (EPCR) is enabled. The presently claimed molecule is transported to the nuclei of endothelial cells *via* the conjugate described. Baumgartner teaches the successful expression of genes that have been transported to the nucleus of the endothelial cell(s) (gene transcription can only occur in the nucleus of endothelial cells).

The appellants submit that the data of Baumgartner provides: (1) well-defined biochemical or clinical end points that would clearly indicate whether the therapy is having a desired effect; and (2) that gene therapy was not considered a highly experimental area of research at the time of filing the present application. Furthermore, the gene therapy protocol used in the Baumgartner reference clearly shows success (directly refuting the Recombinant DNA Advisory Committee (RAC) assertion that expectations of current gene therapy protocols are over sold without any success; **as cited by the Examiner in Touchette *et al. as of January 1996, over two years prior to the submitted Baumgartner reference).***

As stated on pages 9 and 10 of the specification, delivery is enhanced in areas of inflammation or coagulation processes. Serum stimulates nuclear translocation, but is not required. Such conditions are typically more pronounced in areas where delivery is desired. Thus, a conjugate of the agent binding to the EPCR and the molecule to be delivered that is administered intramuscularly, **will congregate in, and target areas of inflammation or coagulation.** Alternatively, the compositions may be delivered to cells *in vitro*, which can remain in culture or be returned to an individual. The number of molecules to be administered will be determined empirically, based on the efficiency of uptake, the number of cells that will be delivered in the composition, and other variables normally considered in determining an

effective amount (such as the *in vivo* half-life of the conjugate, and the efficiency of uptake, both of which can be determined without undue experimentation).

The Board's attention is drawn to the decision dated July 22, 2002, in U.S.S.N. 08/28,306 (Appeal No. 1998-0667). An issue on appeal was whether claims drawn to a method of making a pseudocapsid from papovavirus major antigen, excluding minor capsid antigens, then mixing the empty pseudocapsid with exogenous material, to form a delivery system, was enabled for delivery to cells. The Board found at page 6 of the decision that "it appears that the examiner's concern is directed more to his belief that the field of gene therapy itself is non-enabled as opposed to the use of the present pseudocapsid technology in the field of gene therapy being non-enabled .... Since we have no separate stated position specific to the present pseudocapsid technology, the examiner's rejection cannot be sustained." The patent application should issue shortly. It appears that the Examiner has followed the same course in rejecting the claims in this application. This rejection should not be sustained.

iii. Legal Standard for Written Description

Both the written description and enablement requirements are defined by 35 U.S.C. §112, first paragraph, which states that the patent specification must contain "a written description of the invention, and of the manner and process of making and using it ... [such] as to enable any person of ordinary skill in the art to which it pertains ... to make and use the same ... "The purpose of the written description requirement is to prevent a patentee from later asserting that he invented something which he did not. Thus the patentee must "recount his invention in such detail that his future claims can be determined to be encompassed within his original creation." *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1561, 19 USPQ 2d 1111, 1115 (Fed. Cir. 1991). The

purpose of the enablement requirement is to teach those of ordinary skill in the art how to make and use the invention without "undue experimentation." The specification does not need to teach what is already known in the art. The specification is enabled if one of ordinary skill in the art only engages in routine experimentation to make the invention.

For many years the leading case for the written description requirement in the biotechnology and pharmaceutical arts was *Eli Lilly v. Univ. of Calif. Board of Regents* in *Regents of University of California v. Eli Lilly & Co.,* 119 F.3d 1559, 43 USPQ 2d. 1398 (Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089 (1998). The Federal Circuit evaluated whether claims to recombinant production of human insulin in U.S. Patent No. 4,652,525 (herein referred to as "the '525 patent") met the written description requirement. The court determined that the specification failed to comply with the written description requirement for only disclosing a single species of DNA encoding non-human insulin.

In *Enzo Biochem*, the Federal Circuit held that the written description requirement can be met by a functional description of claimed materials, if coupled with a known or disclosed correlation between function and structure. *Enzo Biochem, Inc. v. Gen-Probe,* 296 F.3d 1316, 63 USPQ 2d. 1609 (Fed. Cir. 2002) ("*Enzo II*"). The Federal Circuit held that a patentee complied with the written description requirement by depositing biological material in a public depository. The specification described the nucleotide sequence in terms of its ability to bind to *N. gonorrhoeae.* The patent had issued with no written description rejection. Nevertheless, the Federal Circuit had determined in *Enzo I* that, because the inventor had not described the actual nucleotide sequence of the probes in the patent specification, the written description was inadequate as a matter of law. In *Enzo II*, the Federal Circuit rejected its narrow interpretation of *Eli Lilly* that the disclosure of the sequence was always necessary, and instead adopted a broader

interpretation of the types of disclosures that comply with the written description requirement. The court adopted provisions from the Guidelines issued by the U.S. Patent and Trademark Office that state that the written description requirement can be met by a functional description of claimed materials, if coupled with a known or disclosed correlation between function and structure. The court found that the written description requirement was met when, in the knowledge of the art, the disclosed functionality is sufficiently correlated to a particular, known structure.

This standard has been reviewed and clarified further in the recent decision of *Amgen Inc. v. Hoechst Marion Roussel, Inc. and Transkaryotic Therapies, Inc.*, 314 F.3d 1313, 65 USPQ 2d. (Fed. Cir. 2003). This decision was the appeal of a lengthy district court ruling on validity, infringement, and enforceability of five Amgen patents relating to production of erythropoietin (EPO), a hormone that controls formulation of red blood cells. Amgen's EPO is sold under the brand name EPOGEN®. Amgen asserts that Hoechst (now Aventis Pharmaceuticals, Inc.) and Transkaryotic Therapies ("TKT") infringed U.S. Patent No. 5,547,933; 5,618,698; 5,621,080; 5,756,349; and 5,955,422, due to the filing of TKT's Investigational New Drug Application (INDA). All of the patents shared the same disclosure. TKT recombinantly produced EPO using a method that differed from the method used by Amgen and described in the patents. TKT inserted a promoter which caused the expression of ordinarily unexpressed endogenous (or "native") EPO DNA in human cells to produce the EPO.

The Federal Circuit upheld the lower court's claim construction and its decision that the claims comply with the written description and enablement requirements of 35 U.S.C. §112. In rendering its decision, the Court continued in the manner of *Enzo II* and applied a broad interpretation of the types of disclosures that comply with the written description requirement.

TKT asserted that claims did not meet the written description requirement since Amgen had failed to described the use of all mammalian and vertebrate cells, relying on the earlier *Lilly* decision.

Relying heavily on the expert testimony provided in the District Court proceeding, the Federal Circuit held that this description adequately supported the claims covering EPP made using the genus vertebrate or mammalian cells.

One question that arose out of these proceedings was whether or not Amgen's disclosure of one means of producing synthetic EPO in mammalian cells, namely exogenous DNA expression, entitles it to claim all EPO produced by mammalian cells in culture, or all cultures vertebrate cells that produce EPO. The district court in this case found that "the specification need teach only one mode of making and using a claimed composition." *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 126 F.Supp.2d. 69, 160, 57 USPQ 2d. 1515 (D. Mass. 2001).

iv. Rejection of Claims 1, 4, 6, 7, 9, 10, 13, 14, 18, 19, 21-23, and 25 Under 35 U.S.C. §112, First Paragraph, as Lacking Written Description

The specification demonstrates reduction to practice *via* a single embodiment; an antibody to EPCR. Other molecules are known, can be made, and could be easily used. Binding to the endothelial protein C receptor (EPCR) is key to defining the agent as claimed. The specification describes the structure of the claimed agents by providing examples of domains known to interact with the well characterized EPCR (thereby implicitly illustrating the chemical properties, i.e., hydrogen bond acceptor and donor sites arranged specifically of the claimed agents). These elements define the agents based on the claimed interaction with the well defined and characterized EPCR. Although the agents may be organic, inorganic, proteins, or even

nucleic acids, specific binding is achieved through complementary interactions (see, for example, page 5, lines 18-31, and page 6, lines 1-23).

"One of skill in the art would have recognized that the spectrum of antibodies which bind to antigens were implicitly disclosed as a result of the isolation of antigen X." Synopsis of Application of Written Description Guidelines, at 60, available at http://www.uspto.gov/web/patents/guides.htm ("Application Guidelines"). The appellant respectfully submits that it is well recognized in the art that while antibodies retain the basic Y-shaped molecule structure, composed of two H (heavy) and two L (light) chains, they are differentiated based upon their antigen binding sites (or CDRs). Different binding sites are generated with different amino acid side chains in these positions, which are commonly known in the art as complementary determining regions, or CDRs, and are located at the end of the variable light and variable heavy chains. It is well established in the art that, based upon the structural features of antibody recognition of an epitope, at least three forces drive antigen/epitope binding: (1) hydrogen bonding between donor-acceptor pairs on the variable regions and the targeted epitope; (2) water molecules that may be present at the antibody-antigen interface contribute to the complex hydrogen bonding pattern between molecules; and (3) numerous van der Waals interactions. These forces provide for the exquisite complementarity at the interface between the antibody and its targeted epitope. The applicant submits these exact forces are what dictate the structure of the claimed agents. Although the agents may be organic, inorganic, proteins, or even nucleic acids, specific binding is achieved through complementary interactions (see, for example page 5, and the description of CDRs). Therefore, in order for the agent to be delivered to the nucleus of endothelial cells, hydrogen bond donor sites, hydrogen bond acceptor sites, and chemical side groups, have to be in the correct spatial location,

orientation, and have the correct charge. The identification and characterization of the EPCR, as described in the specification and prior art, by a combination of primary, secondary and tertiary structure analysis is sufficient for the determination of the structure of the agent, or one can simply screen for binding to the EPCR, since EPCR is well known to those in the field. This identification is parallel to the "isolation of Antigen X," as stated in the example provided in the written description guidelines and quoted above. Therefore, not only has the targeted EPCR been fully characterized (analogous to the isolation and characterization of antigen X), but the forces that drive the complementary interactions between antibody/antigen and compound/RNA are the same. These complementary interactions, as defined by the CDRs (complementarity determining regions) of antibodies, and the complementary region of the claimed agents define their respective structures (*i.e.*, the CDRs provide specificity to the staggeringly large repertoire of antibodies with different antigen-binding capabilities and are the basis for the immune system's ability to recognize virtually all foreign antigens) in view of their targeted epitope. It is no coincidence that the antibody/epitope and the claimed compound/substrate interactions and structures are defined using the same, well acknowledged and understood term in the art: "complementarity." Both, antibodies and nucleic acid hybridizing compounds are now designed based upon known epitope/antigen and nucleic acid. Once these "substrate" structures are known, complementary interactions lie at the core of producing a well defined structure that is able to recognize and bind to the target (*i.e.*, like a "lock and key" – see below).

Furthermore, the appellants have disclosed that agents harboring the Gla domain of protein C may be used to direct binding to EPCR (see page 6, lines 12-23), further illustrating just how well characterized endothelial protein C receptor is, and it defines the structure of the

agent that targets and binds to them (for example, Gla domains). The same issues discussed above, as they relate to complementary interactions, apply to Gla domains.

It will help, perhaps, to view the EPCR as a "lock" and the agent as the "key," wherein the shape of the interior of the lock is defined by hydrophobic, hydrogen bonding, and electrostatic forces provided by the amino acids of the receptor. The key (agent) will only fit into the lock if it is able to "complement" these forces. The analogy to a "lock and key" is an important one because if one can conceptualize the role of the predetermined and defined EPCR in demanding a specific structure of the binding agent, then one will recognize that the compound in demanding a specific structure of the binding agent, then one will realize that the compound structure is clearly defined.

As stated in M.P.E.P. §2173.05(t), which describes the standard to be applied to compounds and compositions, "a compound of unknown structure may be claimed by a combination of physical and chemical characteristics." See Ex parte Brian, 118 USPQ 242 (Bd. App. 1958). M.P.E.P. §2173.05(t) further states that "a compound may also be claimed in terms of the process by which it is made without raising an issue of indefiniteness." The structural features common to the members of the claimed genus can only be determined once the hydrogen bonding arrangement of the target molecule (in this case, EPCR) is derived. Once the "target" is derived, the binding pocket of the EPCR can be easily inserted into any number of commercially available computer programs and the structural features of a binding agent be determined. The structure of the agent is clearly limited based on the requirement for it to be complementary to the EPCR target.

With regard to molecules to be derived, the Examiner stated that the specification only teaches biotinylated-anti-EPCR antibody and poly-L-lysine conjugated anti-EPCR antibody.

The applicants submit that these are merely examples of what can be delivered to the nucleus of endothelial cells using the claimed methods. The specification clearly describes methods that can be used to determine translocation of molecules to the nucleus. As described at the bottom of page 7 and top of page 8, translocation to the nucleus can be readily assayed using proper and well known reagents that can be detected on the cell and/or in the nucleus of the cell (for example, surface labeled EPCR and luciferase gene(s) bound to polylysine modified anti-EPCR monoclonal antibodies). As defined by the specification and claims as originally filed, many molecules can be delivered; the key is the molecule binding to the EPCR. One of ordinary skill in the art could readily ascertain, without undue experimentation, whether or not molecules are translocated to the nucleus of endothelial cells. Furthermore, other examples have been presented which clearly illustrate techniques and methods commonly used at the time of filing the present application. For example, the Experimental Procedures section of the specification clearly describes techniques one would/could use to isolate nuclei and nuclear extracts, and assay for translocation of molecules transported *via* EPCRs.

(c) Rejection Under 35 U.S.C. §102

i. The Legal Standard

The legal requirement under 35 U.S.C. §102(b) requires that the prior art disclosure each claimed element in a single reference. *Glaxo Inc. v. Novopharm Ltd.*, 52 F.2d 1043, 34 USPF [?] 2d. 1565 (Fed. Cir. 1995); *cert. denied*, 516 U.S. 998 (195). The disclosure in the reference need not be express, but may anticipate by inherency where it would be appreciated by one of ordinary skill in the art. *Id.*

Under the principles of inherency, if the prior art necessarily functions in accordance with, or includes, the claimed limitations, it anticipates. *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 51 USPQ 2d. 1943 (Fed. Cir. 1999). Inherency may not be established by probabilities or possibilities. See *Scaltech Inc. v. Retec/Tetra, L.L.C.*, 178 F.3d 1378, 51 USPQ 2d. 1055 (Fed. Cir. 1999). The mere fact that a certain thing may result from a given set of circumstances is not sufficient to establish inherency. *Id.* Where a reference provides a general disclosure such that one skilled in the art would not necessarily recognize that an element is disclosed in the reference, such a reference is not one that inherently anticipates the element. *See. i.e., Finnegan Corp. v. U.S. Int'l. Trade Comm'n.,* 180 F.3d 1354, 1365, 51 USPQ 2d. 1001, 1009 (Fed. Cir. 1999). In relying on the theory of inherency, the Examiner must provide a basis in fact or in technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teaching of the applied reference. *Ex parte Levy*, 17 USPQ 2d. 1461, 1464 (Bd. Pat. App. & Int'f. 1990).

ii. Rejection of Claims 13, 15, 20 and 22 under 35 U.S.C. §102(b) as lacking novelty over U.S. Patent No. 5,225,537 to Foster *et al.* ("Foster")

The issue here is whether or not Foster inherently discloses of a molecule binding to the EPCR conjugated to a molecule to be delivered. Foster teaches DNA constructs for the expression of hybrid phospholipid-binding properties wherein the coding sequences of a phospholipid-binding domain of a lipocortin and a gla-domainless vitamin K-dependent protein are joined. The gla-domain for protein C extends from amino acid 1 of the mature form of protein C to amino acid 45 (see column 7, lines 45-47). There is no indication in Foster that one should deliver a hybrid phospholipid-binding protein to large vessel endothelial cells. Furthermore, the target cells of Foster are ***transfected*** with *DNA sequences* encoding hybrid

protein C. Once transfected, the cells provide the machinery to produce the conjugate encoded by the delivered DNA sequence(s). Transfection is directed to the general uptake, incorporation, and expression of recombinant DNA sequence(s). Transfection is directed to the general uptake, incorporation, and expression of recombinant DNA by eukaryotic cells (if it is analogous to bacterial transformation; often a naturally occurring phenomenon in bacteria). Foster fails to teach the delivery of conjugated molecules to the nucleus of endothelial cells ***via*** **an EPCR receptor.** Foster fails to teach an agent that selectively binds to an EPCR receptor. At a minimum, this is true because any DNA sequence intended to be used for transfection, cannot be used to selectively bind to an EPCR. The delivery methods taught in Foster refer to DNA transfection. Upon transfection, the cells are then cultivated for proper expression of the protein of interest. Nowhere in Foster is there a teaching of using the protein for delivery to endothelial nuclei *via* EPCR receptors.

iii. Rejection of claims 13, 15, 20 and 22 under 35 U.S.C. §102(b) as lacking novelty over U.S. Patent No. 5,571,786 to Eibl *et al.* ("Eibl")

Eibl clearly teaches in Example 3 (see column 6) that protein C was ***mixed*** with thrombin gel and allowed to react (i.e., to form activated protein C, ***not to form a conjugate***). It should be noted that claim 13 is directed, in part, to a "***fusion protein or conjugate*** formed by ***indirect*** binding by a positively charged polymer, chimeric antibody or streptavidin" (emphasis added). **Nowhere** in Example 3 does it state/teach "attachment to thrombin coupled to CNBr-Sepharose 4B." Example 3 **does** teach reacting protein C with thrombin for 3 hours under continuos shaking. One of ordinary skill in the art will clearly recognize that reacting thrombin and protein C does not result in any kind of attachment or conjugated molecule. Instead, the reaction merely serves to generate an activated form of protein C (not conjugated).

iv. Rejection of claims 13-15, 20 and 22 under 35 U.S.C. §102(b) as lacking in novelty over PNAS 93:10212-10216, 1996, by Stearns-Kurosawa *et al.* ("Stearns-Kurosawa")

Stearns-Kurosawa describes a fluorescein-labeled anti-mouse IgG **to ascertain the effect of antibodies on the binding of** fl-APC, fl-cho-protein C, or biotin-PC to E7 cells, EA.hy926 cells, and HUVECs (i.e., diagnostic fluorescein-labeled anti-mouse IgG antibodies).

Diagnostic agents have been excluded from claims 13 and 14. Therefore Stearns-Kurosawa cannot disclose the subject matter of claims 13 and 14. Given the broadest interpretation of the term, "diagnostic," one of ordinary skill in the art will readily recognize that fluorescein-labeled anti-mouse IgG falls within the scope of a diagnostic agent. The appellants had submitted a Merriam-Webster Dictionary definition of the term, "diagnosis," wherein version "3a" is directed to an analysis of the nature of a situation <diagnosis of engine trouble> (submitted with response mailed on May 12, 2003).

In summary, based upon the foregoing discussion, none of the prior art anticipates the claimed conjugates since (1) Foster does not teach a conjugate of a molecule to be delivered to an endothelial cell; (2) one of ordinary skill in the art would readily agree that merely mixing protein C with thrombin gel may result in a activating protein C, but would not form a conjugate; and (3) Stearns-Kurosawa discloses a diagnostic reagent which is excluded from the claimed subject matter. Therefore, the claims on appeal are free from prior art.

(d) The Examiner has failed to individually examine the independent claims.

It is well established that each claim must be separately examined for patentability. It is not enough, as here, to look at a single independent claim and reject all claims. No rationale has

been presented as to why the subject matter of claims 2, 3, 4, 10, 13-15, and 25 are not enabled (all directed to methods using, or compositions having, conjugates containing various binding agents and various molecules to be delivered). No rationale has been presented as to why the subject matter of claims 5-9 and 16-21 are not enabled (all directed to methods using, or compositions having, conjugates with varying molecules to be delivered. Claims 22-24 are directed to various coupling means; whereas claims 11 and 12 are directed to the administration of conjugates to *in vivo* or *in vitro* sites.

These claims must be considered separately because each group contains different elements (*i.e.*, various means for coupling, various molecules to be delivered, methods to be used *in vitro* versus *in vivo*, and conjugates between various molecules to be delivered and various binding agents). The issues are different with regard to enablement of a method to selectively deliver a conjugate to the nucleus of endothelial cells of large vessels *in vitro* (claim 11) or *in vivo* (claim 12). The issues are different with regard to enablement of constructing a conjugate composition having different coupling means, different molecules to be delivered, and differences in the conjugate, itself (i.e., conjugates between various molecules to be delivered and various binding agents).

As claimed, various coupling means may be used as part of each conjugate. The claims directed to various conjugates should be recognized for separate consideration. Claims 11 and 12 are directed to the administration of conjugates to *in vivo* or *in vitro* sites and should be recognized for separate consideration.

IX. Summary and Conclusion

The claimed methods and compositions are directed to selectively-delivering molecules to the nucleus of endothelial cells of the large vessels, by administering a conjugate of (1) an agent binding selectively to endothelial protein C receptor (EPCR) which promotes uptake by the cell and transfer into the nucleus and (2) the molecule to be delivered to large vessel endothelial cells. The conjugate binds to the EPCR, the conjugate is endocytosed, and the molecule is thereby delivered to the cytoplasm or to the nucleus of the large vessel endothelial cells (see claim 1 as originally filed and the Examples set forth in the specification). The conjugate may be delivered by directly contacting the endothelial cells of large vessels with the conjugate or by catheterization with blood vessels formed by the endothelial cells (page 10, lines 15-18).

As discussed in this Appeal Brief, none of the cited prior art can be legitimately used in a 35 U.S.C. §102(b) rejection, as the Examiner has done. Furthermore, the Appellants have demonstrated a reduction to practice in the application with respect to one molecule, an antibody to the receptor. The Examiner has cited many articles to support his assertion that gene therapy is not enabled, but no evidence for why results obtained with an antibody for the receptor would not be predictive of other molecules which bind. Furthermore, the appellants have submitted references that clearly show that gene therapy was proven to be successful in the treatment of endothelial cells.

For the foregoing reasons, Appellant submits that the claims 1-25 are patentable.

In light of the foregoing, appellants respectfully submit that all pending claims are definite and supported by the application as filed. Therefore, it is respectfully requested that the Board reverse each of the pending rejections.

Respectfully submitted,

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X. Claim Appendix

1. (previously amended) A method for selectively delivering a molecule to the nucleus of endothelial cells of large vessels, comprising

administering a conjugate to large vessel endothelial cells, wherein the conjugate comprises an agent binding selectively to endothelial protein C receptor (EPCR) which causes uptake by the cell and transfer into the nucleus conjugated to the molecule to be delivered.

2. (original) The method of claim 1 wherein the conjugate is formed between the molecule to be delivered and an antibody to EPCR.

3. (original) The method of claim 1 wherein the conjugate is formed between the molecule to be delivered and activated protein C.

4. (original) The method of claim 1 wherein the conjugate comprises a chimeric antibody binding to the molecule to be delivered and to EPCR.

5. (original) The method of claim 1 wherein the molecule to be delivered is a nucleic acid molecule and the nucleic acid molecule is a gene or cDNA under the control of a promoter expressed in the nucleus of an endothelial cell and the nucleic acid molecule is delivered by directly contacting the endothelial cells of large vessels with the nucleic acid molecule conjugate or by catheterization to the endothelial cells.

6. (original) The method of claim 5 wherein the nucleic acid molecule is selected from the group consisting of triplex forming oligonucleotides, ribozymes, guide sequences for ribozymes, and antisense.

7. (previously amended) The method of claim 1 wherein the molecule to be delivered is selected from the group consisting of drugs, proteins and diagnostic agents, wherein the drug is not a nucleic acid.

8. (original) The method of claim 1 wherein the molecule to be delivered is a protein.

9. (original) The method of claim 8 wherein the protein is a transcription factor.

10. (original) The method of claim 1 wherein the molecule to be delivered is coupled to the agent which binds to EPCR by molecules selected from the group consisting of streptavidin and biotin, and molecules having multiple positive charges.

11. (original) The method of claim 1 wherein the conjugate is administered to large vessel endothelial cells in culture or isolated from an individual.

12. (previously amended) The method of claim 1 wherein the conjugate is administered directly to an individual.

13. (previously amended) A conjugate of an agent binding selectively to endothelial protein C receptor (EPCR) selected from the group consisting of protein C, activated protein C, antibodies reactive with EPCR and fragments of the antibodies reactive with EPCR binding to EPCR, and a molecule selected from the group consisting of nucleic acids, proteins, and drugs to be delivered to a large vessel endothelial cell, wherein the molecule is not a diagnostic label, wherein the conjugate is a chemical conjugate, fusion protein or conjugate formed by indirect binding by a positively charged polymer, chimeric antibody or streptavidin.

14. (previously amended) A conjugate of

an agent binding selectively to an endothelial protein C receptor (EPCR) selected from the group consisting of an antibody to EPCR, or a fragment or recombinant molecule based on the antibody to EPCR, to

a molecule to be delivered to a large vessel endothelial cell, wherein the molecule is not a diagnostic label,

wherein the conjugate is a chemical conjugate, fusion protein or conjugate formed by indirect binding by a positively charged polymer, chimeric antibody or streptavidin.

15. (previously amended) The conjugate of claim 13 wherein the conjugate is formed between the agent to be delivered and activated protein C.

16. (original) The conjugate of claim 13 wherein the molecule to be delivered is a nucleic acid molecule in combination for means for directly contacting the nucleic acid molecule conjugate directly with the endothelial cells of large vessels, wherein the means are for in vitro treatment of the cells or by catheterization to the endothelial cells.

17. (original) The conjugate of claim 16 wherein the nucleic acid molecule is a gene or cDNA under the control of a promoter expressed in the nucleus of an endothelial cell.

18. (original) The conjugate of claim 16 wherein the nucleic acid molecule is selected from the group consisting of triplex forming oligonucleotides, ribozymes, guide sequences for ribozymes, and antisense.

19. (currently amended) The conjugate of claim 13 wherein the molecule to be delivered is a drug, wherein the drug is not a nucleic acid or protein.

20. (original) The conjugate of claim 13 wherein the molecule to be delivered is a protein.

21. (previously amended) The conjugate of claim 20 wherein the protein is a transcription factor.

22. (previously amended) The conjugate of claim 20 comprising a coupling means which binds the molecule to be delivered to the agent which binds EPCR.

23. (original) The conjugate of claim 22 wherein the coupling means is a positively charged polymer or molecule.

24. (original) The conjugate of claim 22 wherein the coupling means is streptavidin-biotin.

25. (previously amended) The conjugate of claim 13 comprising a chimeric antibody which binds to EPCR and to the molecule to be delivered.